Organofluorine Compounds

International Edition: DOI: 10.1002/anie.201609715
German Edition: DOI: 10.1002/ange.201609715

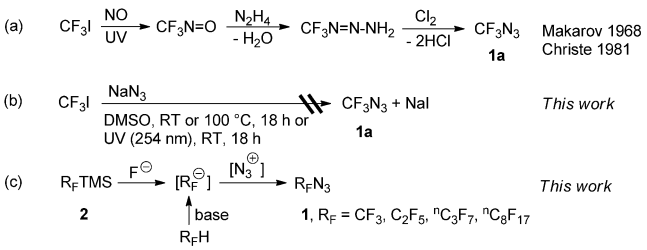
Azidoperfluoroalkanes: Synthesis and Application in Copper(I)-Catalyzed Azide–Alkyne Cycloaddition

*Zsófia E. Blastik, Svatava Voltrová, Václav Matoušek, Bronislav Jurásek, David W. Manley, Blanka Klepetářová, and Petr Beier**

Abstract: *We report an efficient and scalable synthesis of azidotrifluoromethane (CF_3N_3) and longer perfluorocarbon-chain analogues (R_FN_3; $R_F = C_2F_5$, $^nC_3F_7$, $^nC_8F_{17}$), which enables the direct insertion of CF_3 and perfluoroalkyl groups into triazole ring systems. The azidoperfluoroalkanes show good reactivity with terminal alkynes in copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC), giving access to rare and stable N-perfluoroalkyl triazoles. Azidoperfluoroalkanes are thermally stable and the efficiency of their preparation should be attractive for discovery programs.*

Organic compounds containing trifluoromethyl and perfluoroalkyl motifs find numerous applications as crop protection agents, pharmaceuticals, and functional materials.[1] In drugs, for example, the trifluoromethyl group is introduced mainly to increase metabolic stability and lipophilicity (which leads to better membrane permeability) and to modulate the pK_a of neighboring ionizable functional groups. It is also capable of imparting weak C–F···X interactions.[1a,b,2] Perfluoroalkyl (R_F) groups are most commonly attached directly to aromatic rings; however, more recently, there has been a surge of interest in the synthesis of heteroatom-bound structures (R_FO, R_FS).[1d,3] In comparison, the R_FN motif is relatively rare and its chemistry has hardly been explored. This is either due to low stability or difficulty in accessing such compounds.[4] Filling this niche offers new prospects for the creation of compounds with unique physical, chemical, and biological properties.

Organic azides are valuable intermediates in synthetic chemistry. Their ability to react with nucleophiles or electrophiles, to access nitrene chemistry, or to act as dipoles in cycloadditions, underscores their versatility.[5] Copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC), for example, is widely used across medicinal chemistry, polymer science, and chemical biology.[6] However, a drawback of azides is their potentially explosive nature. Azidotrifluoromethane (**1a**) was prepared by Makarov[7] and later by Christe[8] in two steps from trifluoronitrosomethane (Scheme 1a). Intuitively, such a compound might be considered explosive; however; **1a** is relatively thermally stable and explodes only when heated above 300 °C.[7,9] Nevertheless, the preparation of **1a** from trifluoronitrosomethane, which is toxic and requires gas handling techniques, has precluded the use of **1a** in synthesis.



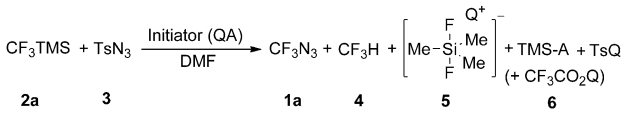
Scheme 1. Synthetic strategies toward azidoperfluoroalkanes (**1**).

Improving the synthesis of **1a** in order to explore and develop its synthetic utility was the focus of this research. The reaction of CF_3I with sodium azide under thermal or photolytic conditions ($S_{RN}1$ mechanism) proved unsuccessful (Scheme 1b). However, a formal polarity reversal of the reaction constituents did offer a more fruitful approach (Scheme 1c). CF_3TMS (**2a**, Ruppert–Prakash reagent) is a well-known and easily accessible reagent for nucleophilic trifluoromethyl addition. Upon activation by Lewis bases, it transfers the CF_3 group to a variety of electrophiles.[10] Importantly, we found that stable electrophilic azides such as *p*-toluenesulfonyl azide (**3**, TsN_3) or nonaflyl azide (NfN_3) are competent partners in this reaction. Longer carbon chain azidoperfluoroalkanes are not known, and our aim was to prepare them in an analogous manner from trimethyl(perfluoroalkyl)silanes (**2**) or from 1*H*-perfluoroalkanes (Scheme 1c). Some azidopolyfluoroalkanes have been synthesized through the reaction of sodium azide with polyfluoroalkenes[11] or halodifluoromethyl compounds.[12]

Optimization of the synthesis of CF_3N_3 (**1a**) was carried out using the strategy outlined in Scheme 1c. Unlike the reactions of silane **2a** with carbonyl compounds, where a catalytic amount of initiator is sufficient (the catalytic cycle is maintained by the intermediate alkoxide), in our case, an equimolar amount of the initiator was necessary. Anhydrous fluoride- or oxygen-containing initiators were explored and the reaction was monitored by ^{19}F NMR to determine yields of **1a** and the side products fluoroform (**4**) and difluorosilicate **5** (Table 1). With K_2CO_3 in DMF, silane **2a** was converted slowly at ambient temperature or within one

[*] Z. E. Blastik, Dr. S. Voltrová, B. Jurásek, Dr. D. W. Manley, Dr. B. Klepetářová, Dr. P. Beier
The Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences
Flemingovo nam. 2, 16610 Prague 6 (Czech Republic)
E-mail: beier@uochb.cas.cz
Dr. V. Matoušek
CF Plus Chemicals s.r.o.
Kamenice 771/34, 625 00 Brno (Czech Republic)
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under http://dx.doi.org/10.1002/anie.201609715.

Table 1: Optimization of the CF_3N_3 synthesis.

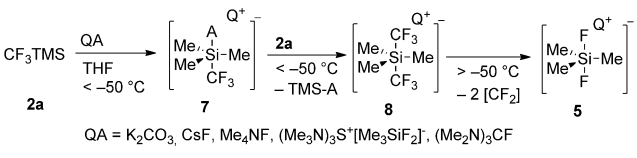


Entry	Initiator (QA)	**2a**/**3**/QA [mmol]	Temp. [°C]	Time [h]	Yield [%][a] **1a**, **4**, **5**, **6**
1	K_2CO_3	3:1:3	RT	18	31, 2, 36, 3
2	K_2CO_3	1:3:1	RT	18	26, 2, 8, 2
3	K_2CO_3	1:3:1	60	1	25, 3, 8, 3
4	Cs_2CO_3	1:3:1	RT	1	20, 8, 8, 30
5	K_3PO_4	1:1:1.2	RT	18	17, 22, 17, –
6	Me_3N^+—O^-	1:1:1.2	RT	18	6, 16, 0, –
7	$^nBu_4N^+(OAc)^-$	1:1:1.2	RT	18	39, 10, 41, –
8[b]	TBAT	1:1:1	−78 to RT	2	25, 3, 20, –
9[b]	TBAF	1:1:1	−78 to RT	1	10, 34, 3, –
10	CsF	1:1:1	RT	1	27, 5, 38, –
11	CsF	2:1:1	RT	1	52, 2, 29, –
12	CsF	1:1:1	−60	18	65, 13, 0, –
13	CsF	1.2:1:1.2	−60 to −30	4	**79**, 9, 0, –

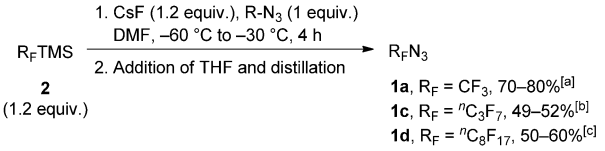
[a] Yield determined by ^{19}F NMR, using $PhCF_3$ as an internal standard. [b] THF was used instead of DMF.

hour at 60 °C, providing low yields of **1a**, traces of **4** and potassium trifluoroacetate (**6**), and significant amounts of difluorosilicates **5** (Table 1, entries 1–3). The use of Cs_2CO_3 led to faster conversion of **2a** at room temperature but the trifluoroacetate side product dominated (entry 4). K_3PO_4 behaved in a similar manner to K_2CO_3 (entry 5), whilst other oxygen-containing initiators afforded low yields of **1a** (entries 6 and 7). THF-soluble fluoride initiators did not bring any improvement (entries 8 and 9). Eventually, the highest yield of **1a** was achieved using a slight excess of **2a** and CsF in DMF at low temperature (entry 13). The formation of byproducts deserves a mention. Fluoroform **4** originates from the reaction of activated silane **2a** with residual water, which can be suppressed by ensuring rigorously anhydrous conditions and conducting the reaction on a larger scale. Difluorosilicate **5** is a product of the thermal decomposition of bis(trifluoromethyl)silicate **8**, which is formed from the reaction of **7** (activated form of **2a**) with excess **2a** (Scheme 2). This process and some of the compounds, such as **5**, **7**, and **8**, have been previously described.[13] Compounds **7** and **8** are known to be capable of nucleophilic CF_3 transfer.[13] The formation of **1a** is also accompanied by the byproducts TMS-A and TsQ.

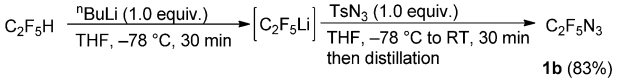
The synthesis of **1a** was scaled up to 10–20 mmol without difficulty, however, isolation was complicated by its low boiling point (lit. b.p. −28.5 °C).[8] Pure samples were obtained by distillation from the reaction mixture (using K_2CO_3 as an initiator), but only in low yields (< 10 %); ^{13}C NMR (101 MHz, $CDCl_3$) of **1a**: $\delta = 122.0$ ppm (q, $^1J_{CF} = 267.6$ Hz). An improved isolation method suitable for the preparative synthesis of **1a** involved the addition of THF or $CDCl_3$ to the reaction mixture and distillation after the reaction with **3** and CsF (Scheme 3). The THF solution of **1a** (containing TMS-F) with concentrations of **1a** below 0.3 M can be conveniently stored in a closed flask at ambient temperature for at least five weeks. Alternatively, the reaction mixture in DMF can be used directly for further transformations (see below). Longer-carbon-chain derivatives of CF_3N_3 were synthesized in an analogous manner from silanes **2** (Scheme 3). The reactivity of silanes **2c** and **2d** was significantly lower than that of **2a**, which necessitated the use of a more reactive electrophilic azide (NfN_3). Azides **1c** and **1d** are also volatile compounds and were purified by distillation with THF. Compound **1d** is insoluble in THF between its melting temperature (ca. −60 °C) and −20 °C, and thus could be obtained in pure form. Azidopentafluoroethane (**1b**, $C_2F_5N_3$) was prepared in a different manner. This involved the preparation of C_2F_5Li by treating pentafluoroethane with ^{n}BuLi. The lithiated intermediate displayed good stability in THF at −78 °C.[14] Further reaction with **3** afforded **1b** in a good yield (Scheme 4). Stability experiments (sealed NMR tube, ^{19}F NMR monitoring) revealed no decomposition of **1b** or **1d** after 80 min at 150 °C. Thus azides **1** are safe to use in chemical synthesis under ambient or moderately harsh conditions.



Scheme 2. Activation and decomposition of **2a**. ^{19}F NMR (376 MHz, $CDCl_3$) of **5** (QA = CsF): $\delta = -60.3$ ppm (s).



Scheme 3. Synthesis of azidoperfluoroalkanes **1**. Yields were determined by ^{19}F NMR, using $PhCF_3$ as an internal standard. [a] R = Ts. Yield range of 8 preparations on a 10–20 mmol scale. [b] R = Nf. Yield range of 2 preparations on a 1–2 mmol scale. [c] R = Nf. Yield range of 3 preparations on a 1–2 mmol scale.



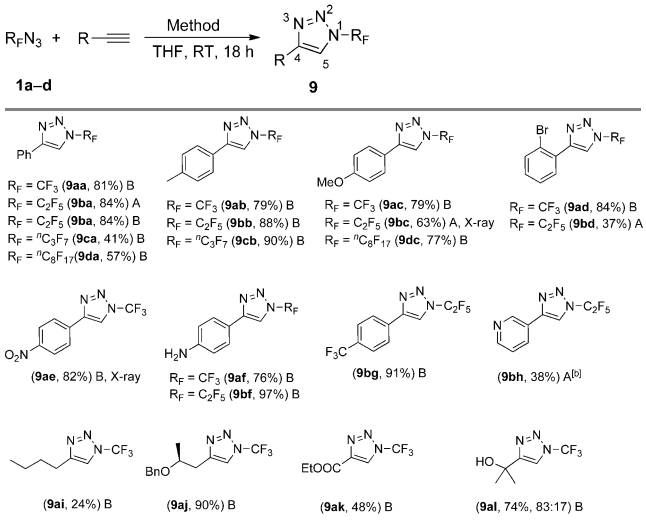
Scheme 4. Synthesis of azidopentafluoroethane (**1b**).

Having developed an attractive and scalable synthesis of **1a** and its higher perfluoroalkyl analogues, we turned our attention to exploring their reactivity. CuAAC generally affords 1,4-disubstituted triazoles with high selectivity;[6b] however, there are no reports of azide–alkyne cycloaddition with perfluoroalkyl azides. Additionally, *N*-perfluoroalkyl triazoles are very rare. One report describes the formation of a modest amount of *N*-trifluoromethyl triazole in a mixture with *N*-trifluoromethyl aziridines upon the addition of CH_2N_2

to a perfluorinated imine,[15] and another demonstrates electrophilic trifluoromethylation of triazoles to afford a mixture of regioisomeric *N*-trifluoromethyl triazoles in low yields.[16] Some *N*-polyfluoroalkyl triazoles have been prepared through non-regioselective thermal cycloaddition of 1-azido-1,1,2,3,3,3-hexafluoropropane and methyl 3-azido-2,2,3,3-tetrafluoropropanoate,[17] and most recently through regioselective CuAAC of 1-azido-2-chloro-1,1,2-trifluoro-2-iodoethane with alkynes.[11c] 1-Substituted-4-(trifuoromethyl)-1*H*-1,2,3-triazoles have been obtained through cycloaddition of azides with trifluoromethylacetylenes[18] or CF_3CHN_2 with isocyanides.[19]

Azidoperfluoroalkanes **1a–d** (THF solutions) displayed excellent reactivity in CuAAC at ambient temperature to form novel *N*-perfluoroalkyl triazoles (**9**; Table 2). Two different methods were used: the widely employed catalytic copper(II) sulfate with sodium L-ascorbate in aqueous

Table 2: Substrate scope for CuAAC of azides **1a–d** with terminal alkynes.[a]

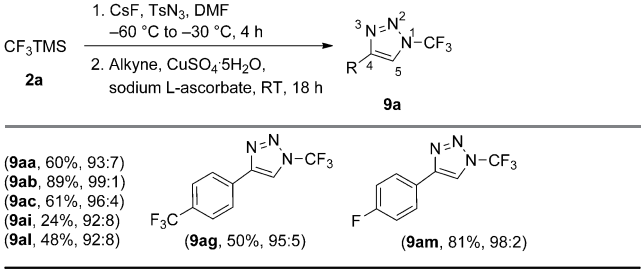


[a] Reaction conditions: alkyne (0.5 mmol), R_FN_3 (0.6 mmol), Method A [$CuSO_4{\cdot}5H_2O$ (10 mol%), sodium L-ascorbate (10 mol%), H_2O (0.1 mL)] or Method B [CuMeSal (1–5 mol%)], THF (3–4 mL), RT, 18 h. [b] 60 °C. CuMeSal = copper(I) 3-methylsalicylate. Compound number, yield of isolated product, and the ratio of 1,4- to 1,5-cycloaddition product (determined by ^{19}F NMR spectroscopy) are shown in parentheses.

THF (method A) or catalytic copper(I) 3-methylsalicylate (CuMeSal) in THF (method B). A variety of aromatic terminal alkynes substituted with electron-withdrawing or -donating groups, as well as heteroaromatic and aliphatic terminal alkynes with halogen, alkoxycarbonyl, hydroxy, and amino groups, participated efficiently in these cycloaddition reactions. Exclusive formation of 1,4-disubstituted triazoles was observed with the single exception of compound **9al**, which afforded a mixture of the 1,4- and 1,5-isomers in an 83:17 ratio. Compound **9ai** was isolated in a rather low yield due to its volatility. Products **9** are stable solids or oils that are amenable to purification by crystallization or column chromatography on silica gel. Crystal structures of **9bc** and **9ae** were determined and clearly show the molecular structure. A [D_6]DMSO solution of **9aa** was stable in the presence of 5 equiv of D_2O, HCl, or NaOD at RT for 18 h. In NaOD, exchange of the aromatic hydrogen atom on the triazole ring for deuterium was detected.

In the case of *N*-trifluoromethyltriazoles **9a**, a one-pot two-step method was developed. This consists of the reaction of **2a** with CsF and **3** in DMF at low temperature, followed by the addition of alkyne, an aqueous solution of $CuSO_4$, and sodium ascorbate, and warming of the reaction mixture to ambient temperature in a closed reaction vessel. Under these conditions, triazoles **9a** were formed in yields comparable with the two-pot process (Table 3). The one-pot method provides the benefit of obviating the need for handling volatile azide **1a**, however, the regioselectivity was generally lower (except for **9al**) than for the two-pot process.

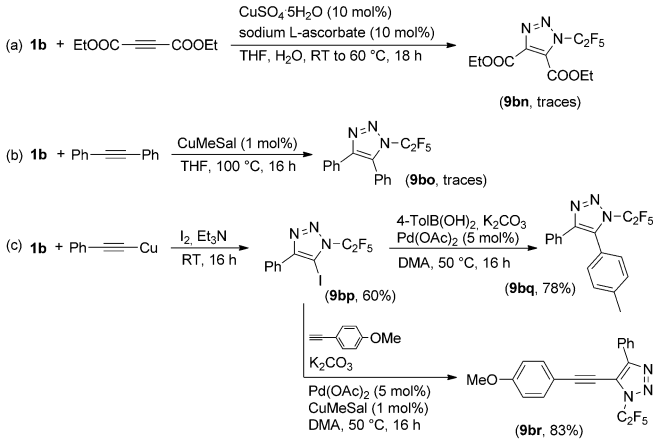
Table 3: One-pot, two-step synthesis of *N*-trifluoromethyl triazoles from **2a**.[a]



[a] Reaction conditions: CF_3TMS (1.2 mmol), CsF (1.2 mmol), TsN_3 (1.0 mmol), DMF, −60 °C to −30 °C, 4 h; alkyne (1.2 mmol), $CuSO_4{\cdot}5H_2O$ (10 mol%), sodium L-ascorbate (10 mol%), RT, 18 h.

A competition experiment revealed that **1b** reacts approximately two-fold faster at the beginning of the reaction than its non-fluorinated analogue 1-azidoethane in CuAAC with 4-ethynyltoluene (Figure S1 in the Supporting Information).

In contrast to terminal alkynes, internal alkynes reacted sluggishly with **1b** even at elevated temperature (Schemes 5a,b). To access 4,5-disubstituted triazoles, an alternative



Scheme 5. Synthesis of 4,5-disubstituted *N*-perfluoroalkyl triazoles.

strategy was devised. Reaction of phenyl copper acetylide with **1b** in the presence of iodine afforded iodotriazole **9bp** in a good yield (Scheme 5c). Triazole **9bp** was partially deiodinated during column chromatography purification on silica gel. Iodotriazoles have previously been prepared from rather unstable iodoalkynes or in situ prepared iodoalkynes from alkynes and *N*-iodomorpholine·HI.[20] Our approach uses stoichiometric amounts of copper but is simple and inexpensive. Suzuki–Miyaura coupling of **9bp** with arylboronic acid and Sonogashira coupling with an arylacetylene provided 4,5-disubstituted triazoles **9bq** and **9br** in good yields (Scheme 5c).

In summary, reactions of perfluoroalkyl carbanion equivalents with electrophilic azides led to the formation of azidoperfluoroalkanes **1** in a preparatively useful method. The method is operationally simple and inexpensive, which should enable the introduction of azidoperfluoroalkanes on the scale required for discovery programs for the first time. The azidoperfluoroalkanes underwent CuAAC with terminal alkynes to form novel *N*-perfluoroalkyl triazoles, with the option of converting them into 4,5-disubstituted triazoles. This work opens new chemical space for investigation of the properties and reactivity of azidoperfluoroalkanes, which represent underexplored but potentially promising fluorinated building blocks.

Acknowledgements

This work was supported by the Czech Academy of Sciences (Research Plan RVO: 61388963) and by the Initial Training Network, FLUOR21, funded by the FP7 Marie Curie Actions of the European Commission (FP7-PEOPLE-2013-ITN-607787).

Keywords: azides · click reactions · fluorine · perfluoroalkanes · triazoles

[1] a) *Fluorine in pharmaceutical and medicinal chemistry*, Imperial College Press, London, **2012**; b) I. Ojima, *Fluorine in Medicinal Chemistry and Chemical Biology*, Wiley-Blackwell, New York, **2009**; c) J.-P. Bégué, D. Bonnet-Delpon, *Bioorganic and medicinal chemistry of fluorine*, Wiley-Interscience, Hoboken, **2008**; d) P. Kirsch, *Modern Fluoroorganic Chemistry*, *2nd ed.*, Wiley-VCH, Weinheim, **2013**; e) J. Wang, M. Sanchez-Rosello, J. L. Acena, C. Del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432–2506; f) D. O'Hagan, *J. Fluorine Chem.* **2010**, *131*, 1071–1081; g) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320–330; h) W. K. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359–4369; i) Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Acena, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev.* **2016**, *116*, 422–518.

[2] K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881–1886.

[3] B. J. Jelier, J. L. Howell, C. D. Montgomery, D. B. Leznoff, C. M. Friesen, *Angew. Chem. Int. Ed.* **2015**, *54*, 2945–2949; *Angew. Chem.* **2015**, *127*, 2988–2992.

[4] a) G. Kloeter, K. Seppelt, *J. Am. Chem. Soc.* **1979**, *101*, 347–349; b) W. J. Middleton, *J. Org. Chem.* **1984**, *49*, 4541–4543; c) A. F. Baxter, K. O. Christe, R. Haiges, *Angew. Chem. Int. Ed.* **2015**, *54*, 14535–14538; *Angew. Chem.* **2015**, *127*, 14743–14746.

[5] a) S. Bräse, C. Gil, K. Knepper, V. Zimmermann, *Angew. Chem. Int. Ed.* **2005**, *44*, 5188–5240; *Angew. Chem.* **2005**, *117*, 5320–5374; b) *Organic Azides: Syntheses and Applications*, Wiley, Chippenham, **2010**.

[6] a) C. Wang, D. Ikhlef, S. Kahlal, J.-Y. Saillard, D. Astruc, *Coord. Chem. Rev.* **2016**, *316*, 1–20; b) E. Haldón, M. C. Nicasio, P. J. Pérez, *Org. Biomol. Chem.* **2015**, *13*, 9528–9550; c) M. Meldal, C. W. Tornoe, *Chem. Rev.* **2008**, *108*, 2952–3015; d) J. E. Hein, V. V. Fokin, *Chem. Soc. Rev.* **2010**, *39*, 1302–1315.

[7] S. P. Makarov, A. Y. Yakubovich, A. S. Filatov, M. A. Enlin, T. Y. Nikiforova, *Zh. Obshch. Khim.* **1968**, *38*, 709–715.

[8] K. O. Christe, C. J. Schack, *Inorg. Chem.* **1981**, *20*, 2566–2570.

[9] Decomposition of CF_3N_3 to N_2, F_2 and FCN when heated in a molybdenum tube above 1120 K was reported: H. Bock, R. Dammel, D. D. DesMarteau, *Z. Naturforsch. B* **1987**, *42*, 308–314.

[10] a) G. K. S. Prakash, A. K. Yudin, *Chem. Rev.* **1997**, *97*, 757–786; b) X. Liu, C. Xu, M. Wang, Q. Liu, *Chem. Rev.* **2015**, *115*, 683–730.

[11] a) C. G. Krespan, B. E. Smart, *J. Org. Chem.* **1986**, *51*, 320–326; b) C. G. Krespan, *J. Org. Chem.* **1986**, *51*, 332–337; c) J. Dai, Z. Li, T. Wang, R. Bai, *Org. Biomol. Chem.* **2016**, *14*, 4382–4386.

[12] a) S. A. Postovoi, Y. V. Zeifman, I. L. Knunyants, *Russ. Chem. Bull.* **1986**, *35*, 1183–1186; b) T. G. Archibald, K. Baum, *J. Org. Chem.* **1990**, *55*, 3562–3565; c) T. Hiramatsu, Y. Guo, T. Hosoya, *Org. Biomol. Chem.* **2007**, *5*, 2916–2919; d) S. A. Lermontov, A. G. Polivanova, S. B. Shkavrov, *Russian J. Gen. Chem.* **2010**, *80*, 1646–1651.

[13] a) A. Kolomeitsev, V. Movchun, E. Rusanov, G. Bissky, E. Lork, G.-V. Röschenthaler, P. Kirsch, *Chem. Commun.* **1999**, 1017–1018; b) N. Maggiarosa, W. Tyrra, D. Naumann, N. V. Kirij, Y. L. Yagupolskii, *Angew. Chem. Int. Ed.* **1999**, *38*, 2252–2253; *Angew. Chem.* **1999**, *111*, 2392–2393.

[14] N. E. Shevchenko, V. G. Nenajdenko, G.-V. Röschenthaler, *J. Fluorine Chem.* **2008**, *129*, 390–396.

[15] P. L. Coe, A. G. Holton, *J. Fluorine Chem.* **1977**, *10*, 553–564.

[16] K. Niedermann, N. Fruh, R. Senn, B. Czarniecki, R. Verel, A. Togni, *Angew. Chem. Int. Ed.* **2012**, *51*, 6511–6515; *Angew. Chem.* **2012**, *124*, 6617–6621.

[17] S. A. Lermontov, S. V. Shkavrov, A. N. Pushin, *J. Fluorine Chem.* **2000**, *105*, 141–147.

[18] T. Abe, G. H. Tao, Y. H. Joo, R. W. Winter, G. L. Gard, J. M. Shreeve, *Chem. Eur. J.* **2009**, *15*, 9897–9904.

[19] S. Wang, L.-J. Yang, J.-L. Zeng, Y. Zheng, J.-A. Ma, *Org. Chem. Front.* **2015**, *2*, 1468–1474.

[20] J. E. Hein, J. C. Tripp, L. B. Krasnova, K. B. Sharpless, V. V. Fokin, *Angew. Chem. Int. Ed.* **2009**, *48*, 8018–8021; *Angew. Chem.* **2009**, *121*, 8162–8165.

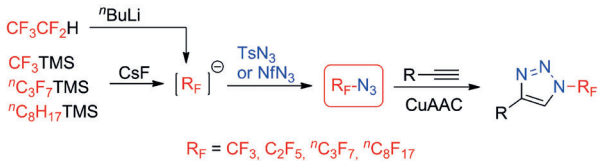
Manuscript received: October 4, 2016
Final Article published: ■■ ■■, ■■■■

Communications

Organofluorine Compounds

Z. E. Blastik, S. Voltrová, V. Matoušek, B. Jurásek, D. W. Manley, B. Klepetářová, P. Beier* ——— ■■■■–■■■■

Azidoperfluoroalkanes: Synthesis and Application in Copper(I)-Catalyzed Azide–Alkyne Cycloaddition



No longer chemical curiosities: Azidoperfluoroalkanes were conveniently prepared from perfluoroalkyl carbanion precursors and electrophilic azide reagents. The azidoperfluoroalkanes show good stability and good reactivity with terminal alkynes in copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC), giving access to rare and stable *N*-perfluoroalkyl triazoles.